REMARKS

The Examiner rejected claims 1-7, while withdrawing claim 8 from consideration. Applicants cancelled claims 2 and 8 without prejudice. Claims 1 and 3-7 have been amended herein to recite a mouse. In addition, claim 1 has been amended to recite that the mouse is homozygous for the disrupted IEX-1 sequence and lacks expression of an IEX-1 polypeptide, and claim 7 has been amended recite that the mouse homozygous for the disrupted IEX-1 sequence lacks expression of an IEX-1 polypeptide. Applicant's specification fully supports these amendments. For example, original claim 2 discloses that the non-human mammal can be a mouse. In addition, page 2, lines 21-22 and lines 29-30 disclose that the animal can be homozygous and can lack expression of an IEX-1 polypeptide. Thus, no new matter has been added.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-7 under 35 U.S.C. § 112, first paragraph, because "the specification, while being enabling for a transgenic, homozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of its genome, wherein the mouse exhibits blood pressure that is higher than a mouse that does not have a disruption in IEX-1 in its genome and expresses no IEX-1 protein, and a transgenic, heterozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of the genome, wherein breeding said transgenic heterozygous mice result in a transgenic, homozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of its genome, wherein the mouse exhibits blood pressure that is higher than a mouse that does not have a disruption in IEX-1 in its genome, wherein the mouse exhibits blood pressure that is higher than a mouse that does not have a disruption in IEX-1 in its genome and expresses no IEX-1 protein," allegedly does not reasonably provide enablement for any non-human mammal or any heterozygous non-human mammal comprising a disruption of the IEX-1 locus in its genome, wherein the mammal exhibits blood pressure that is higher than a control mammal that does not comprise the disruption.

Applicants respectfully disagree. To further prosecution, however, the pending claims have been amended to recite a mouse. In addition, independent claim 1 has been amended to recite that the mouse is homozygous for the disrupted IEX-1 sequence and lacks expression of an IEX-1 polypeptide. Independent claim 7 has been amended to recite that the mouse homozygous for the disrupted IEX-1 sequence lacks expression of an IEX-1 polypeptide. As the Examiner appears to acknowledge, Applicants' specification fully enables the pending claims as amended.

In light of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-7 under 35 U.S.C. § 103(a) as being unpatentable over the De Keulenaer *et al.* reference (*Cir. Res.*, 90:690-696 (2002)) in view of Capecchi (*Trends in Genetics*, 5:70-76 (1989)). Specifically, after characterizing the cited references, the Examiner stated that the American Heritage online dictionary defines hypertrophy as a nontumorous enlargement of an organ or a tissue as a result of an increase in the size rather than the number of constituent cells: muscle hypertrophy. In addition, the Examiner stated that the De Keulenaer *et al.* reference teaches that there is a cardiomyocyte hypertrophic response following mechanical strain. At this point, the Examiner speculates as follows:

> [t]his means that following mechanical strain, the size of cardiomyocytes would increase in size. If the cardiomyocytes increased in size, then the diameter of the blood vessel would decrease. If the blood vessel diameter decreased, there would then be more mechanical strain to pump blood into tissues. More mechanical strain would then lead to an even more narrow blood vessel diameter. If this is the case, then an increase in blood pressure would be the outcome in this scenario. Ultimately, then, it could be conceived that a transgenic mouse comprising a disruption in IEX-1 could have blood pressures 5, 10, 20, or 30 mm of Hg above that of a mouse with no disruption in IEX-1.

The Examiner then concludes that it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to make a mouse comprising a

disruption in IEX-1 in its genome, wherein the mouse exhibits high blood pressure as a result of cardiomycocyte hypertrophy.

Applicants respectfully disagree. First, the cited references provide no indication that an increase in cardiomyocyte size decreases blood vessel diameter. Notwithstanding this, the cited references provide no suggestion that a person having ordinary skill in the art should make a mouse containing a disrupted IEX-1 sequence and having a level of blood pressure that is higher than the level observed in a control mouse mammal lacking the disruption. The fact that overexpression of IEX-1 was reported to abolish cardiomyocyte hypertrophy induced by mechanical strain provides no indication or suggestion that disrupting IEX-1 expression would result in increased blood pressure. Thus, the presently amended claims are not obvious.

In light of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

Applicants submit that claims 1 and 3-7 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone Applicants' attorney if such would further prosecution. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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